



PATENT  
Attorney Docket No. 61169

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Mary R. Flack et al.

Group Art Unit: 1205

Serial No. 08/379,872

Examiner: J. Goldberg

Filed: January 27, 1995

For: Gossypol For The Treatment  
Of Cancer

37 CFR § 1.132 DECLARATION

Assistant Commissioner For Patents  
Washington, D.C. 20231

FEB 18 1997

Sir:

1200  
GROUP 1500

I, Mary R. Flack, declare as follows:

1. I am a co-inventor of the subject matter that is disclosed and claimed in the matter of the above-identified application, and I am an expert in the field of the present invention as evidenced by the attached copy of my *curriculum vitae*.

2. While I was not listed as co-author on the accompanying Wu et al. publications, I am nonetheless co-inventor of the subject matter that is disclosed and claimed in the above-identified application. This is because, Richard Knazek, Marcus Reidenberg and myself were each involved in the conception of the invention that is disclosed and claimed in the above-identified application. In this regard, I was not listed as co-author on the accompanying Wu et al. publication, since I was not directly involved with the laboratory studies reported in the Wu et al. publication, even though I was involved with clinical studies relating to the present invention.

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3. I have read and understand the Declaration of Richard Knazek and I agree with what he has stated regarding the participation by Dr. Wu and Dr. Chik.

4. The sole co-inventors of the subject matter that is disclosed and claimed in the above-identified application are Richard Knazek, Marcus Reidenberg and Mary Flack (myself).

5. I hereby declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patents issued therefrom.

Date: 1/28/97

By: Mary R. Flack  
Mary R. Flack

# CURRICULUM VITAE

## Mary Ruth Flack

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### Home:

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Date and Place of Birth: September 27, 1958, Chicago Illinois

Marital Status: Married

### Education:

1980 B.S., *cum laude*, Wheaton College, Wheaton, IL  
1984 M.D., Wayne State University School of Medicine, Detroit, MI

### Professional History:

1984-1985 Intern, Internal Medicine, Northwestern University, Chicago, Illinois  
1985-1987 Resident, Internal Medicine, Northwestern University, Chicago, Illinois  
1987-1990 Medical Staff Fellow, Developmental Endocrinology Branch, NICHD, NIH, Bethesda, MD  
1990-1995 Senior Clinical Investigator, Developmental Endocrinology Branch, NICHD, NIH, Bethesda, MD  
1994-1995 Faculty, Federal Fellowship in Reproduction, NICHD, NIH & Bethesda Naval Hospital, Bethesda, MD  
1995- Director, Clinical Research Division, Endocrine Group, Parke Davis Pharmaceutical Research, Ann Arbor, MI

### Board Certification:

National Board of Medical Examiners, 1985

American Board of Internal Medicine:

Internal Medicine, 1988

Endocrinology, Diabetes, and Metabolism, 1991

### Investigational Protocols:

NIH90-CH-32 1990-93 The use of gossypol in adrenal cancer, principal investigator  
NIH93-CH-002 1993-95 Biologic properties of FSH and related molecules, principal investigator

NCI93-CO-200	1993-95	Adriamycin, VP16, and mitotane in metastatic adrenal cancer, associate investigator
NIH93-CH-223	1993-95	Autoimmune premature ovarian failure: a controlled trial of alternate-day prednisone therapy, associate investigator
NCI94-CO-156	1994-95	Adriamycin, VP16, and mitotane in metastatic renal cell cancer, associate investigator
Z01-HD00616-14	1994-95	Structure, function, and physiology of glycoprotein hormones, principal investigator
PD1001-001	1995-96	A randomized, double-blind, active-controlled, multicenter study assessing the contraceptive effectiveness associated with transvaginal administration of 3 dose combinations of norethindrone acetate and ethinyl estradiol, Drug Director

Committees:

Clinical Research Institutional Review Board, NICHD, NIH, member, 1991-1993

Professional Societies:

American Association for the Advancement of Science  
 American Federation of Clinical Research  
 American Pituitary Association  
 American Society for Clinical Pharmacology and Therapeutics  
 Endocrine Society  
 New York Academy of Sciences  
 Sigma XI  
 Women in Endocrinology

Patents and Investigational New Drugs (IND):

FDA IND - #32,864 - Gossypol acetic acid  
 U.S. Patent - #07-551-353 - Gossypol acetic acid for the treatment of cancer

Editorial:

Reviewer, *Annals of Internal Medicine*  
 Reviewer, *Journal of Clinical Endocrinology and Metabolism*  
 Reviewer, *Life Sciences*

Publications:

1. Wehmann RE, Blithe DL, Flack MR, Nisula BC. Metabolic clearance rate and urinary clearance rate of purified  $\beta$ -core. *J Clin Endo Metab* 69:510-517, 1989.
2. Doppman J, Miller DL, Petronas N, Oldfield EH, Merriam G, Frank SJ, Flack MR, Weintraub BD, Gordon P. The diagnosis of acromegaly: The value of inferior petrosal sinus sampling. *Am J Radiol* 154: 1075-1077, 1990.
3. Lash RW, Desai RK, Zimmerman C, Flack MR, Yoshida T, Wondisford FE, Weintraub BD. Site-directed mutagenesis of the human TSH- $\beta$  gene reveals regions of the protein important in TSH synthesis and secretion. *J Endocrinol Invest* 15:255-263, 1992.
4. Flack MR, Oldfield EH, Cutler GB, Chrousos GP, Zwieg MH, Malley JD, Loriaux DL, Nieman LK. Urine free cortisol in the high dose dexamethasone suppression test for the differential diagnosis of Cushing syndrome. *Ann Int Med* 116:211-217, 1992.
5. Flack MR, Pyle RG, Mullens NM, Lorenzo B, Wu YW, Knazek RG, Nisula BC, Reidenberg MM. Gossypol in the treatment of metastatic adrenal cancer. *J Clin Endocrinol Metab* 74(4)1019-1024, 1993.
6. Flack MR, Froehlich J, Bennet AP, Anasti JN, Nisula BC. Site-directed mutagenesis defines the individual roles of the glycosylation sites on follicle-stimulating hormone. *J Biol Chem* 269:14015-14020, 1994
7. Flack MR, Bennet AP, Froehlich J, Anasti JN, Nisula BC. Increased biologic activity due to basic isoforms in recombinant FSH produced in a human cell line. *J Clin Endocrinol Metab* 79: 756-760, 1994
8. Anasti JN, Flack MR, Froehlich J, Nelson LM, and Nisula BC. hTSH stimulation of the hFSH receptor: a novel mechanism for the precocious puberty of severe juvenile hypothyroidism. *J Clin Endocrinol Metab*, in press
9. Valove FM, Finch C, Froehlich J, Flack MR. Receptor binding and signal transduction are dissociable functions requiring different sites on follicle-stimulating hormone. *Endocrinology*, 135:2657-2661, 1994.
10. Anasti JN, Flack MR, Froehlich J, Nelson LM. The use of recombinant human gonadotropin receptors to search for Immunoglobulin G-mediated premature ovarian failure. *J Clin Endocrinol Metab*, 80:824-828, 1995
11. Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. *Am J Ob/Gyn*, in press.

Submitted for publication:

1. Froehlich J, Anasti JN, Flack MR. Site-directed mutagenesis of the thioredoxin-like region of follicle-stimulating hormone defines its role in receptor activation. *Mol Cell Endocrinol*
2. Zweig MH, Flack MR. The use of receiver operating characteristic curves in the differential diagnosis of Cushing syndrome. *Clinical Chemistry*
3. Anasti JN, Froehlich J, Nelson LM, Flack MR. Mutations of the third cytosolic loop of the human follicle stimulating hormone receptor cause constitutive activation. *J Clin Endocrinol Metab*
4. Passaro MD, Anasti JN, Froehlich J, Flack MR. A single residue in the FSH $\beta$  carboxyterminus is a determinant of FSH binding specificity. *J Clin Endocrinol Metab*

Invited Chapters:

1. Lash RW, Desai RK, Flack MR, Wondisford FE. Site-directed mutagenesis of the human TSH- $\beta$  gene: Factors affecting subunit combination and secretion. In: *Horizons in Endocrinology*, Maggi M, Geenan V (eds), Vol. 2 New York: Raven Press, 13-18, 1991.
2. Flack MR, Bennet AP, Nisula BC. Production of recombinant hFSH in a human cell line: Biologic and immunologic properties. In: *Horizons in Endocrinology*, Maggi M, Geenen V (eds.) Vol. 2, New York: Raven Press, 26-31, 1991.
3. Flack MR, Chrousos GP. Cancer of the Adrenal Cortex. In: *Cancer Medicine*, 3rd ed., Holland JP (ed.), Malvern PA: Lea & Febiger, 1993; 1147-1153.
4. Flack MR, Oldfield EH, Cutler GB, Chrousos GP, Zwieg MH, Malley JD, Loriaux DL, Nieman LK. Urine free cortisol in the high dose dexamethasone suppression test for the differential diagnosis of Cushing syndrome. *1993 Yearbook of Med.*, St. Louis: Mosby, Inc., 513-515, 1994.
5. Flack MR, Pyle RG, Mullens NM, Lorenzo B, Wu YW, Knazek RG, Nisula BC, Reidenberg MM. Gossypol in the treatment of metastatic adrenal cancer. *1994 Yearbook of Drug Therapy*, St Louis: Mosby, Inc., 201-208, 1995.
6. Nelson LM, Anasti JN, Flack MR. Premature Ovarian Failure. In: *Reproductive Endocrinology, Surgery, and Technology*, Adashi EY, Rock JA, and Rosenwaks Z (eds), Philadelphia: Lippincott-Raven Publishers, 1393-1410, 1996.
7. Flack MR, Chrousos GP. Cancer of the Adrenal Cortex. In: *Cancer Medicine*, 4th ed., Holland JP (ed.), Malvern PA: Lea & Febiger, in press.

Oral presentations/Invited talks:

1. Flack MR, Loriaux DL, Nieman LK. Urine free cortisol: A better measure of response to the dexamethasone suppression test in Cushing's syndrome. Oral presentation, Endocrine Society, 1988.
2. Flack MR. Production of recombinant FSH in a human cell line. Invited speaker, Endocrine Grand Rounds, University of Maryland, 1989.
3. Flack MR, Bennet AP, Nisula BC. Biologic and immunologic properties of recombinant hFSH. Invited speaker, Endocrinology under 35, 1990.
4. Flack MR, Bennet AP, Froehlich J, Anasti JN, Nisula BC. Selective mutagenesis of the glycosylation sites of FSH; Effects on secretion, conformation, and biologic potency. Oral presentation, Endocrine Society, 1992.
5. Flack MR, Valove FM, Finch C, Froehlich J. Follicle-stimulating hormone signal transduction is distinct from receptor binding and each requires a different site on the hormone. Invited speaker, X Ovarian Workshop, 1994
6. Flack MR. Hirsutism: The long and the short of it. Endocrinology for the General Practitioner, University of Maryland, 1995.
7. Flack, MR, Kempfert N, Anderson F, Mishell D, Thomas M, Williams R, Rowan J. Vaginal administration of contraceptive steroids reduces total steroid exposure with improved cycle control. Am Soc Reprod Med, 1996.

Abstracts:

1. Wehmann RE, Blithe DL, Flack MR, Akar AH, Nisula BC. Metabolic clearance rate and urinary clearance rate of  $\beta$ -core in humans. Poster presentation, Serono Glycoprotein Hormone Symposium, 1989.
2. Wehmann RE, Flack MR, Nisula BC. Disparity between  $\beta$ -core levels in serum and urine in pregnancy. Poster presentation, Endocrine Society, 1989.
3. Lash RW, Wondisford FS, Yoshida T, Flack MR, Weintraub BD. Site-directed mutagenesis of the human TSH beta gene: Factors affecting subunit combination and secretion. Oral presentation, Endocrine Society, 1989.
4. Flack MR, Wu YW, Pyle RG, Mullens NM, Nisula BC, Reidenberg, MM, Knazek, RG. Treatment of adrenocortical carcinoma with gossypol. Poster presentation, American Association for Cancer Research, 1990.
5. Flack MR, Pyle RG, Mullens NM, Lorenzo B, Wu YW, Knazek RG, Nisula BC, Reidenberg MM. Gossypol in the treatment of metastatic adrenal cancer. Poster presentation, Endocrine

Society, 1991.

6. Flack MR, Bennet AP, Froehlich J, Anasti JN, Nisula BC. Selective inhibition of FSH glycosylation by site-directed mutagenesis: Effects on secretion and biologic activity. Poster presentation, American Federation of Clinical Research, 1992.
7. Anasti JN, Flack MR, Froehlich J, Nisula BC. A novel mechanism for the macroorchidism of juvenile hypothyroidism. Poster presentation, Endocrine Society, 1993.
8. Froehlich J, Anasti JN, Flack MR. Site-directed mutagenesis of the thioredoxin-like region in  $\beta$  FSH: Effects on receptor binding and steroidogenic activity. Poster presentation, Endocrine Society, 1993.
9. Valove FM, Finch C, Froehlich J, Flack MR. Site-directed mutagenesis of a critical FSH $\beta$  region elucidates the role of amino acid charge in the action of FSH at the human FSH receptor. Poster presentation, Ovulation Induction:Basic Science and Clinical Advances, 1993.
10. Anasti JN, Flack MR, Froehlich J, Nisula BC. The use of human recombinant FSH receptor to search for IgG mediated premature ovarian failure. Poster presentation, Soc Gyn Invest, 1994.
11. Anasti JN, Froehlich J, Nelson LM, Flack MR. Mutations of the third cytosolic loop of the human follicle stimulating hormone receptor causes constitutive activation. Oral presentation, American Fertility Society, 1994.
12. Flack MR, Finch C, Froehlich J. Site-directed mutagenesis defines the roles of the oligosaccharides of hFSH at the human FSH receptor. Poster presentation, Endocrine Society, 1994.
13. Valove FM, Finch C, Froehlich J, Flack MR. Site-directed mutagenesis defines the role of charged amino acids in the binding of hFSH to the human FSH Receptor. Poster presentation, Endocrine Society, 1994.
14. Passaro MD, Anasti JN, Froehlich J, Ebert LA, Flack MR. Site-directed mutagenesis of amino acid 99 of human FSH yields decreased binding and biologic activity, Poster presentation, Endocrine Society, 1995.